III. REMARKS

Applicants respectfully request reconsideration of this application in view of the above amendments and the following remarks.

1. Status of the Claims

Claims 36-40 are pending in this application. New Claims 41 and 42 have been added in this response. Accordingly, upon entry of the amendments, Claims 36-42 will be pending for examination on the merits.

2. Summary of the Amendments

Claim 36 has been amended in step (a) to replace "identifying" with "selecting." Support for this amendment is found, for example, at page 100, lines 18-21.

Claim 36 has also been amended in steps (a), (b) and (c) to replace "a" with "the" to clarify the antecedent basis for particular terms as kindly suggested by the Examiner.

Claims 36 and 38 have also been amended to delete the term "compound" or "compounds" after the term "ligand."

Additionally, Claim 37 has been amended to recite "to determine the binding affinity of the compound for the cellular receptor" in place of "to determine its affinity for the cellular receptor." Support for this amendment is found, for example, on page 106, lines 27-29.

New Claims 41 and 42 have been added. Support for these claims in found, for example, on page 88, lines 04 to page 89, line 08.

Entry of these amendments is respectfully requested.

3. Restriction Requirement/Election of Species

Applicants respectfully acknowledge that the restriction/election requirement for Claims 36-40 has been made final and that Claim 36 has been withdrawn, in part, from consideration under 35 U.S.C. §121.

Should no prior art be found that anticipates or renders obvious the elected species, Applicants respectfully request that the search be extended and the withdrawn subject matter of Claim 36 be examined on the merits.

4. Objection to the Claims

Claims 36-40 have been objected to, in part, for depending from Claim 36, which is withdrawn, in part, as drawn to non-elected subject matter. Applicants respectfully request that, if no prior art is found that anticipates or renders obvious the elected species of Claim 36, the search be extended to include the withdrawn subject matter of Claim 36 and that Claim 36 be examined in its entirety.

5. Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 36-40 have been rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner has indicated that there is uncertain antecedent basis for the terms "a ligand compound" and "a cellular receptor" in line 20; "a linker compound" in line 26; and "a library of compounds" in line 32.

In response, Applicants have amended the above-identified terms to replace "a" with "the" and to delete the unnecessary term "compounds." In view of these amendments, Applicants believe the antecedent basis for these terms is now clear. Accordingly, this rejection may be withdrawn.

Additionally, the Examiner has indicated that, in Claim 37, it is unclear whether the phase "its affinity" refers to the affinity of the "compound" or the "library." In response, Applicants have amended Claim 37 to clearly indicate that the binding affinity of the compound is being determined. Accordingly, this rejection may also be withdrawn.

6. Rejections Under 35 U.S.C. §112, First Paragraph

A. Written Description Requirement

Claims 36-40 have been rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. Specifically, the Examiner has indicated that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. For the following reasons, this rejection is respectfully traversed.

The Examiner's rejection is based, in part, on the following statements:

> The skilled artisan cannot envision the detailed chemical structure of the encompassed genera of all ligands that bind to a cellular receptor or to cellular receptors that are G-protein coupled receptors or muscarinic receptors, and therefore conception is not achieved until reduction to practice has occurred, regardless of he complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The ligand themselves are required. See Fiers v. Revel, 25 USPQ2d at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, at 1483 (finding claims directed to *mammalian* FGF's were found to be unpatentable due to lack of written description for that broad class, where the specification provided only the *bovine* sequence). Office Action at page 6 (emphasis in original).

By these statements, it appears that there is some confusion regarding what is meant by the term "identifying" as used in step (a). As used by Applicants, this term is intended to mean that one skilled in the art selects a ligand that binds to a cellular receptor for use as a starting material for the presently claimed method. To clarify what is meant, Applicants have amended Claim 36 to replace "identifying" with "selecting."

Thus, to practice the present invention, one skilled in the art merely selects a ligand as a starting material from, for example, the published literature. In this regard, to provide guidance and to comply with the written description requirement, Applicants provided in the specification as originally filed an extensive list of known ligands that bind to cellular receptors. Specifically, the tables and accompanying text on pages 11 to 27 of the specification give hundreds, if not thousands, of specific examples of known ligands for at least 47 different cellular receptors.

Like any other method claim, Applicants are not required to specifically list every possible starting material in the specification that could ever be used in the method in order to meet the written description requirement. All that is required is that Applicants provide adequate representative examples of suitable starting materials. Given the extensive disclosure in Applicants' specification of many hundreds of suitable ligands for scores of cellular receptors, one skill in the art would clearly recognize that the inventors had possession of the claimed method at the time the application was filed. Accordingly, the written description requirement of 35 U.S.C. §122 has been satisfied and this rejection may be withdrawn.

B. Enablement Requirement

Claims 36-40 have been rejected under 35 U.S.C. §112, first paragraph, because the specification allegedly does not enable any person skilled in the art to make and use the invention commensurate in scope with the claims. Specifically, the Examiner has indicated that the specification, while being enabling for ligands taught by the instant specification, does not reasonably provide enablement for all ligands that bind to a cellular receptor. For the following reasons, this rejection is respectfully traversed.

Again, from the Office Action, it appears that there is some confusion regarding what is meant by the term "identifying" as used in step (a). Specifically, the Examiner has indicated that the presently claimed method somehow requires the "experimental discovery of new ligands to any cellular receptor." (Office Action at pages 7-8). This is clearly not necessary or required. By way of illustration, a new method for oxidizing an alcohol does not require the experimental discovery of new alcohols or the explicit disclosure of every possible alcohol that could ever be used in the new method. All that is required is that the skilled artisan be given sufficient information to allow them to select a starting material. In the present case, this requirement is clearly met by the extensive list of known ligands that bind to cellular receptors provided in the tables and text on pages 11 to 27 of the specification.

Additionally, the Examiner has indicated that "the Specification does not disclose a single screening assay for identifying a ligand compound which binds to a cellular receptor, as recited in claim 64[sic]." Office Action at pages 8-9. Again, however, the Examiner is presuming that one skilled in the art must somehow rediscover that which is already known in order to practice the presently claimed method. Compounds that bind to cellular receptors are already known in the art. To practice the claimed method, the skilled artisan can merely select any such compound. Moreover, Applicants do, in fact, make reference to known screening assays in the specification. See, for example, pages 139 to 145 for assays relating to 5HT1 receptors; pages 154 to 155 for assays relating to muscarinic receptors; page 163 for assays relating to AT1 receptors; and pages 172 to 173 for assays relating to β_2 adrenergic receptors. Similar assays are widely known and routinely used by those skilled in the art.

In summary, Applicants' specification gives sufficient information to enable one skilled in the art to select a ligand that binds to a cellular receptor for use in the presently claimed method.

Accordingly, withdrawal of the rejection of Claims 36-40 under 35 U.S.C. §112, first paragraph, is respectfully requested.

7. Rejections Under 35 U.S.C. §102

Claims 36-39 have been rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Halazy et al., *J. Med. Chem.*, **1996**, *39*, 4920-4927. For the following reasons, this rejection is respectfully traversed.

A prior art reference anticipates a claim only if the reference discloses, either expressly or inherently, every limitation of the claim. In the instant case, the Halazy reference does not anticipate the presently claimed invention because it does not teach a library of compounds in which the ligands of the compounds are attached to the linker at different positions of the ligand. More specifically, step (b) of the present method requires that the library be prepared using ligands which each have a reactive functional group at a different position compared to the other ligands used to prepare the library.

In contrast, the Halazy reference discloses compounds that are all attached at the same position of the ligand, i.e., at the 5-hydroxyl residue. See, for example, Scheme 1 on page 4921 and top paragraph in right column on page 4921. Accordingly, this reference cannot anticipate the present invention.

For the foregoing reasons, Applicants respectfully request that the rejection of Claims 36-39 under 35 U.S.C. §102(b) be withdrawn.

8. Rejections Under 35 U.S.C. §103

Claims 36-40 have been rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Halazy et al., *J. Med. Chem.*, **1996**, *39*, 4920-4927, and Englen et al., *Pharmacology & Toxicology*, **1996**, *78*, 59-68. For the following reasons, this rejection is respectfully traversed.

To establish a *prima facie* case of obviousness, the Examiner must make three showings:

(1) First, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference or to combine references in a manner that produces the claimed invention. *See, In re Fine*, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988).

(2) Second, the Examiner must show that the proposed modification of the prior art references had a reasonable expectation of success as determined from the vantage point of one of ordinary skill in the art. *See Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1343, 56 USPQ2d 1641, 1644 (Fed. Cir. 2000). Both the motivation to modify the prior art references, as well as the expectation of success, must come from the prior art, not from applicant's own disclosure. *See, In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).

(3) Lastly, the Examiner must show that the prior art reference or combination of references teach or suggest all the limitations of the claims. *See, In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970).

If the Examiner fails in any of these requirements, he has not established a *prima facie* case of obviousness, and without more, the applicant is entitled to a patent. *See, e.g., Oetiker*, 977 F.2d at 1445, 24 USPQ2d at 1444 (citing *In re Grabiak*, 769 F.2d 729, 733, 226 USPQ 870, 873 (Fed. Cir. 1985)).

In the present case, the Examiner has combined the teachings of the Halazy reference regarding serotonin dimers with the teachings of the Englen reference regarding ligands that bind to muscarinic receptors to arrive at methods of producing dimers of ligands that bind to muscarinic receptors. However, this premise fails to take into consideration the fact that, even when combined, these references do not teach or suggest all the limitations of the present claims. Specifically, step (b) of the present method requires that the library be prepared using ligands which each have a reactive functional group at a different position compared to the other ligands used to prepare the library. The Halazy reference discloses compounds that are all attached at the same position of the ligand, i.e., at the 5-hydroxyl residue. The Englen reference does not disclose dimers of any type. Therefore, when combined these reference do not teach or suggest the presently claimed method which requires that the library be prepared using ligands which have reactive functional groups at a different positions. Moreover, while the Halazy reference may provide some motivation to explore the area of dimers, the references clearly do not provide any specific motivation to modify their teachings in a manner to arrive at the presently claimed invention.

Accordingly, since the cited references do not establish a *prima facie* case of obviousness, the rejection of Claims 36-40 under 35 U.S.C. §103(a) may be withdrawn.

9. Information Disclosure Statement

The Examiner has indicated that the Information Disclosure Statement (IDS) filed on May 22, 2002, for the above-identified patent application allegedly fails to comply with 37 C.F.R. §1.98(a)(3) because it does not include a concise explanation of the relevance of references B7 and B9, which are not in the English language.

In response, Applicants respectfully note that a concise explanation of the relevance of these references was filed with the IDS submitted on May 22, 2002 (see page 2 of the IDS – copy attached). Since Applicants have complied with the requirements of 37 C.F.R. §1.98(a)(3), Applicants respectfully request that the Examiner consider these references and return of an Examiner-initialed copy of the form PTO/1449 to Applicants for these references with the next Office Action on the merits.

10. Conclusion

Reconsideration of this application in view of the above amendments and remarks is respectfully requested. Should the Examiner have any questions regarding this paper or should any issues arise that can be resolved by telephone, the Examiner is encouraged to telephone the undersigned attorney for Applicants at (650) 808-6406.

Respectfully submitted,
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Date: January 20, 2005

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